UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/355,254	02/22/2000	HERMANN WAGNER	C1041/7005	6183

7590 01/08/2003

HELEN C LOCKHART
WOLF GREENFIELD & SACKS
FEDERAL RESERVE PLAZA
600 ATLANTIC AVENUE
BOSTON, MA 02210-2211

EXAMINER	
ZARA, JANE J	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/08/2003

26

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/355,254	Wagner et al
Examiner	**Art Unit**
First Last	1234

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 26, 2000*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *24-39* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *24-29* is/are allowed.

6) ☒ Claim(s) *30-39* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☒ The oath or declaration is objected to by the Examiner. No Declaration submitted

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 12
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office action is in response to the communications filed September 26, 2000 and September 19, 2002, Paper Nos. 7 and 23, respectively.

Claims 24-39 are pending in the instant application.

Election/Restriction

The restriction requirement mailed July 16, 2002, Paper No. 20 has been vacated as indicated in Paper No. 23 (filed September 19, 2002).

Response to Arguments and Amendments

Withdrawn Objections and Rejections

Objection of claims 4-22 under 37 CFR 1.75(a) is hereby withdrawn in light of Applicants' amendments filed September 26, 2000.

Rejection of claims 19-22 under 35 U.S.C. 101 is hereby withdrawn in light of Applicants' amendments filed September 26, 2000.

Rejection of claims 9, 12, 15, 18, 19-22 under 35 U.S.C. 112, second paragraph, is hereby withdrawn in light of Applicants' amendments filed September 26, 2000.

Rejection of claims 1-18 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession

of the claimed invention, is hereby withdrawn in light of Applicants' amendments filed September 26, 2000.

Rejection of claims 1-6, 9, 11, 12, 16, 17, 19 and 20 under 35 U.S.C. 102(e) as being anticipated by Henderson is hereby withdrawn in light of Applicants' amendments filed September 26, 2000.

Rejection of claim 23 under 35 U.S.C. 102(e) as being anticipated by Watson is hereby withdrawn in light of Applicants' amendments filed September 26, 2000.

Rejection of claims 8, 10, 13-15 and 18 under 35 U.S.C. 103(a) as being unpatentable over Henderson and further in view of Davis is hereby withdrawn in light of Applicants' amendments filed September 26, 2000.

Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear which polynucleotide(s) is being referred to for conferring the various (and contradictory) biological effects embodied in the claims (e.g. claim 36 refers to polynucleotides

capable of inducing a Th2 immune response, while claim 38 refers to polynucleotides capable of inducing a Th1 immune response). Further clarification is requested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for modulating immune responses in Balb/c mice following in vivo (i.e. intraperitoneal) administration of a polynucleotide sequence (i.e. ODN 1668) and ovalbumin, does not reasonably provide enablement for modulating an immune response, inducing a cytolytic T lymphocyte response, inducing Th2 and Th1 immune responses, breaking immune tolerance, regulating Th1/Th2 helper cell responses, switching immunoglobulin classes, treating any and/or all autoimmune diseases and inducing tolerance comprising the administration of any antigen in combination with any oligonucleotide listed in claim 30 in any and/or all organisms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods of inducing a cytolytic T lymphocyte response, inducing Th2 and Th1 immune responses, breaking immune tolerance, regulating Th1/Th2 helper cell responses, switching immunoglobulin classes, treating any and/or all autoimmune diseases and

inducing tolerance comprising the in vivo administration (via any route) of any antigen in combination with any oligonucleotide listed in claim 30.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of gene therapy and immunotherapy in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense efficacy in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2.)

Agrawal et al point to various factors contributing to the unpredictability of gene therapy such as antisense therapeutic approaches in vivo, including non-antisense effects attributed to

secondary structure and charge, as well as biological effects exerted by sequence motifs existing within the antisense sequences, all providing for unpredictable in vivo side effects and limited efficacy (e.g. see pages 72-76). Agrawal et al speak to the unpredictable nature of in vivo therapy: "It is therefore appropriate to study each (antisense) oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (see page 80). Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al in its entirety, especially pages 326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic oligonucleotides to target cells).

The unpredictability of immunotherapy using CpG containing oligonucleotides was also addressed by Weiner: "...we still do not understand the molecular mechanisms responsible for the immunostimulatory effects of CpG ODN. All CpG ODN are not alike, and more needs to be learned about the heterogenous responses that occur based on host organism, cell subset, or CpG ODN sequence. Most importantly, we have not yet explored their clinical effects." (See page 461 of Weiner). In addition, McCluskie et al and Blackshear both address the unpredictability between in vitro and in vivo effects of immunomodulatory oligonucleotides (See both documents in their entirety, especially last paragraphs on pages 107 and 112 of Blackshear and last paragraph on page 296 of McCluskie et al).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward methods of inducing a cytolytic T lymphocyte response, inducing Th2 and Th1 immune responses, breaking immune tolerance, regulating Th1/Th2 helper cell responses, switching immunoglobulin classes, treating any and/or all autoimmune diseases and inducing tolerance comprising the in vivo administration (via any route) of any antigen in combination with any oligonucleotide listed in claim 30.

The specification teaches modulation of immune responses in Balb/c mice comprising intraperitoneal administration of ODN 1668 and ovalbumin. One skilled in the art would not accept on its face the examples given in the specification of immunomodulatory effects obtained following the intraperitoneal administration of ODN 1668 and ovalbumin in Balb/c mice as being correlative or representative of the successful induction of a cytolytic T lymphocyte response, induction of Th2 and Th1 immune responses, breaking immune tolerance, regulating Th1/Th2 helper cell responses, switching immunoglobulin classes, treating any and/or all autoimmune diseases and/or induction of tolerance comprising the in vivo administration (via any route) of any antigen in combination with any oligonucleotide listed in claim 30 in view of the lack of guidance in the specification and known unpredictability associated with predetermining the efficacy of oligonucleotides in predictably modulating an immune response in any organism and in treating any and/or all autoimmune diseases. The specification as filed fails to provide any particular

guidance which resolves the known unpredictability in the art associated with in vivo delivery or treatment effects provided by the claimed oligonucleotides.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to methods of inducing a cytolytic T lymphocyte response, inducing Th2 and Th1 immune responses, breaking immune tolerance, regulating Th1/Th2 helper cell responses, switching immunoglobulin classes, treating any and/or all autoimmune diseases and inducing tolerance comprising the in vivo administration (via any route) of any antigen in combination with any oligonucleotide listed in claim 30. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues in vivo whereby treatment the various immunomodulatory effects are provided. Since the specification fails to provide any particular guidance for the successful induction of a cytolytic T lymphocyte response, induction of Th2 and Th1 immune responses, breaking immune tolerance, regulating Th1/Th2 helper cell responses, switching immunoglobulin classes, treating any and/or all autoimmune diseases and/or induction of tolerance comprising the in vivo administration (via any route) of any antigen in combination with any oligonucleotide listed in claim 30 in any organism, and since determination of the factors required such in vivo success is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope claimed.

Allowable Subject Matter

Claims 24-29 are free of the prior art searched.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be

retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SEAN McGARRY
PRIMARY EXAMINER

JZ

December 27, 2002